REMARKS

Applicant respectfully requests entry of the above amendments. Claims 11, 13-16, 19, and 28-29 are pending in this application. Claim 11 is currently amended, and claim 14 is canceled. Claims 13, 15, 16, 19, 28, and 29 are all previously presented. No new matter was added with this amendment.

Claim Rejections

The Office Action rejected the pending claims under 35 USC §103(a) as being unpatentable over Giles-Komar (US7163681), and Pfizer Products Incorporated, WO03/009848, hereinafter Bronk, and in view of Ono et. al. Eur. J. Pharm. Sci. (1999).

The rejection is based partly on Bronk. The US equivalent application for this WO publication is US2003/0139443. The international filing date for this publication was 15July2002 which published 06Feb2003. The filing and publication date of the US equivalent application was 19Jul2002 and 24Jul2003, respectively. Applicant respectfully requests that the citation, Bronk, be disqualified as prior art under 35 USC §103(c), since the citation constitutes prior art only under 35 USC §102(e), and is not anticipatory; (MPEP 706.02(l)(1) and 706.02(l)(2)).

Under §103(c), "subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102...shall not preclude patentability under this section where the subject matter and the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person".

The Bronk application and the instant invention, at the time the instant invention was made, were commonly and wholly owned by Pfizer Inc, since both were subject to an obligation of assignment to Pfizer Inc. Of note, Pfizer Products Incorporated, was a subsidiary of Pfizer Inc.

Hence, since the subject matter of Bronk and the instant invention were commonly owned by Pfizer, via obligation of assignment, at the time of invention, the reference should be disqualified under §103(c) as prior art in a rejection under §103(a). Therefore, Applicant respectfully requests that the Bronk citation be disqualified as art for purposes of the

obviousness rejection under §103(a). Therefore, Applicant provides remarks relative to Giles-Komar and Ono to overcome the §103(a) rejection.

The Office Action relies on Merck v Biocraft 874 F.2d 804 (1989) and In re Mills 470 F2.d 649 (CCPA1972), and Union Oil v Atlantic Richjfield 208 F.3d 989 (2000) to assess all disclosures in the Giles-Komar reference, not just preferred embodiments or specific working examples, relative to a §103 inquiry. Applicant agrees that the specific excipients are listed in the reference. However, what the reference and Action fail to address is predictability and reasonable expectation of success as recited in KSR Intl. v. Teleflex., U.S. 550 U.S. 398 (2007) and In re Kubin and Goodwin 561 F.3d 1351 (2009). Applicant respectfully disagrees with the Action that there are a finite number of solutions per this citation. Examiner has merely shown that cyclodextrins(column 43, lines 20-21) and preservatives (column 43, lines 40-45) are recited as common excipients of a probable stable formulation. In fact, the citation also describes hundreds of other common excipients for said stable formulation. The citation also states that any suitable concentration or mixture of preservative can be used. These concentrations range from 0.001 to 5%. The citation gives no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful, particularly in light of the issues recited by Ono (below) regarding cyclodextrin complexation. Further, there is no suggestion to which excipient(s) would lead to a reasonable expectation of success. Therefore, none are predictable.

Applicant also points Examiner to EP0119737A2 (1984) which states that the addition of cyclodextrin causes a significant increase in absorption, stability, and solubility of the active ingredient and reduces the preserving effect of the preservative (page 2, lines 1-3). The claim, as currently amended, recites that the preservative demonstrates a pharmaceutically acceptable antimicrobial preservative effect. Further, according to EP0199737A2, halogenated phenol derivatives (Table 2, page 12) were shown not to cause precipitation of the drug/cyclodextrin /preservative complex. In contrast, non-halogenated derivatives, e.g., phenethyl alcohol was shown to cause precipitation of the inclusion complex in solution. Therefore, a skilled artisan would not choose a non-halogenated preservative, such as meta-cresol or phenol for preparing a cyclodextrin formulation. Additionally, WO00/12137 recites that typical preservatives are relatively ineffective at

normal concentrations in compositions due to complexation with cyclodextrin. This contrasts Giles-Komar who suggest that any suitable concentration of a preservative can be used for preparing a stable formulation with a cyclodextrin. According to WO00/12137, to avoid complexation with cyclodextrin, a stabilized chlorite (chlorine dioxide), sorbic acid, alkali metal sorbates and mixtures thereof, at about 1% (w/v) were shown to be preferred preservatives (page 4, lines 21-30). The rationale for these preservatives is that they do not form a complex with the cyclodextrin component. The reference also states that commonly used pharmaceutical preservatives are often less effective when used in the presence of cyclodextrins (page 8, lines 10-12). The EP and WO00/12137 citations clearly teach away from the use of non-halogenated preservatives when formulating with cyclodextrin.

Ono recites complexation issues relative to the use of cyclodextrins, particularly as they relate to the solubility and permeation of phenacetin and various benzoic acids. Ono employed phenacetin and benzoic acid derivatives to specifically model cyclodextrin complexation because they were known to form 1:1 inclusion complexes, thereby making modeling assumptions simple. Overall, modeling requires the determination of stability- and permeation-rate constants in free and complexed fractions. Per Ono, cyclodextrin complex permeation rates are significantly affected by the presence of second guest molecules because of competitive inclusion. According to the Action, the theoretical 1:1 inclusion complexation binding affinity calculations would be synonymous and/or obvious with the complexation affinities of a multifaceted formulation, contrary to Ono. Because of the physicochemical and biological properties of a drug, stability constants, permeation rate constants, and competitive inclusion complexation stoichiometry of active drug(s), preservatives, excipients, and cyclodextrins, the skilled artisan would not be able to ascertain the pharmaceutical composition of the instant invention with any predictability or without undue experimentation. In addition, the art actually teaches away from using the non-halogenated phenols when formulating with cyclodextrin because of complexation and precipitant formation of the preservative.

In light of the aforementioned, Applicant disagrees that it would be obvious for a skilled artisan to prepare a pharmaceutical composition, as claimed, in light of Giles-Komar and Ono. As per KSR and Kubin, there must be some semblance of an expectation of success and predictability for obviousness. The art clearly shows that cyclodextrin

complexation is difficult to assess between the cyclodextrin and active drug alone because they do not form 1:1 complexes. Further, the addition of a guest molecule, i.e., a preservative, merely makes the complexation issue even more unpredictable. The art also teaches away from the non-halogenated phenols as preservatives in cyclodextrin compositions because of complexation. The instant invention has overcome the complexation issues of cyclodextrin, active drug, and preservative, while maintaining the preservative effect of the m-cresol. Therefore, Applicant considers the §103 rejection moot and respectfully requests that said claims be allowed to grant.

Respectfully submitted,

Date: Sept. 22, 2010

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